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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/684,026	10/06/2000	Anthony Louis Devico	11076-002001	3193

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INTELLECTUAL PROPERTY / TECHNOLOGY LAW
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EXAMINER
WINKLER, ULRIKE

ART UNIT	PAPER NUMBER
1648	

DATE MAILED: 07/14/2003

22

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/684,026	DEVICO ET AL.	
	Examiner	Art Unit	
	Ulrike Winkler	1648	

-- Th MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 December 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,6-11,13-16 and 18-73* is/are pending in the application.

4a) Of the above claim(s) *18-23 and 25-72* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,6-11,13-16,24 and 73* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *06 October 2000* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *19, 16, 7, 5*
4) ☒ Interview Summary (PTO-413) Paper No(s). *21* .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

The Office apologizes for the delay of the instant response, however, the papers were not matched with the file until the end of May 2003. In an interview summary Paper No. 21 (attached to the instant Office Action) it was indicated that the Finality of the last Office Action Paper NO. 18 is withdrawn because the office did not mail a signed copy of the IDS of Paper No. 16 as indicated in the last Office action.

The Amendment filed December 23, 2002 (Paper No. 20) in response to the Office Action of October 22, 2002 is acknowledged and has been entered. Claim 12 has been cancelled. Claims 1-3, 6-11, 13-16, 18-72 are pending and claims 1-3, 6-11, 13-16 and 24.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

Drawings

Applicants have not provided the drawing corrections as required in Paper No. 12. Correction of the drawings is required.

Double Patenting

Upon review and reconsideration in view of applicants arguments and claim amendments the prior the double patenting rejections withdrawn in the prior Office Action (Paper No. 18) are reinstated in the instant Office Action.

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible

harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-8, 10, 11, and 73 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1 and 3 of U.S. Patent No. 5,518,723 in view of Chackerian et al. (Proceeding of the National Academy of Sciences, March 1999).

Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant invention is directed to a chimeric polypeptide comprising a viral coat polypeptide sequence and a viral receptor. The sequences are linked by an amino acid chain that function to allow formation of an interacting complex between the virus coat polypeptide sequence and receptor polypeptide sequence (specification, page 14, line 23-31). The U.S. Patent No. 5,518,723 discloses CD4-gp120 (claim 1) is drawn to an immunogenic complex comprising gp120 covalently bonded to CD4 so that cryptic epitopes are exposed. The patent includes the complex in a pharmaceutically acceptable carrier. A peptide bond is a covalent bond because it involves the sharing of electrons. Chackerian et al. teach the production of a chimera between a viral coat protein and cell surface receptors for the production of a complex that allows the production of antibodies against the cell surface receptor, which can prevent viral entry into the cell.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to utilize a chimera for the production of the gp120-CD4 complex as taught by DeVico et al. The gp120 and CD4 molecules have a natural affinity for another and form the complex spontaneously. One ordinary skill in the art would have been motivated to make a gp120-CD4 chimera to reduce the process steps in order to achieve the same function. The chimera as taught by Chackerian et al. requires the single process step utilizing affinity purification after the expression of the chimera in an insect cell. One having ordinary skill in the art would have a high expectation of success when expressing the complex as a single polypeptide. The addition of amino acid linkers would have been obvious to the ordinary artisan in order to alleviate potential folding constraints in the chimera. Therefore, the instant invention is obvious over DeVico et al. in view of Chackerian et al.

Claims 1-8, 10, 11, 24 and 73 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 1 of U.S. Patent No. 5,843,454 in view of Chackerian et al. (Proceeding of the National Academy of Sciences, March 1999).

Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant invention is directed to a chimeric polypeptide comprising a viral coat polypeptide sequence and a viral receptor. The sequences are linked by an amino acid chain that function to allow formation of an interacting complex between the virus coat polypeptide sequence and receptor polypeptide sequence (specification, page 14, line 23-31). The U.S. Patent No. 5,843,454 discloses CD4-gp120 (claim 1) is drawn to an immunogenic complex

comprising gp120 covalently bonded to CD4. The patent includes the complex in a pharmaceutically acceptable carrier. A peptide bond is a covalent bond because it involves the sharing of electrons. Chackerian et al. teach the production of a chimera between a viral coat protein and cell surface receptors for the production of a complex that allows the production of antibodies against the cell surface receptor, which can prevent viral entry into the cell.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to utilize a chimera for the production of the gp120-CD4 complex as taught by DeVico et al. The gp120 and CD4 molecules have a natural affinity for another and form the complex spontaneously. One ordinary skill in the art would have been motivated to make a gp120-CD4 chimera to reduce the process steps in order to achieve the same function. The chimera as taught by Chackerian et al. requires the single process step utilizing affinity purification after the expression of the chimera in an insect cell. One having ordinary skill in the art would have a high expectation of success when expressing the complex as a single polypeptide. The addition of amino acid linkers would have been obvious to the ordinary artisan in order to alleviate potential folding constraints in the chimera. Therefore, the instant invention is obvious over DeVico et al. in view of Chackerian et al.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-3, 6-16 and 24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chackerian et al. (Proceeding of the National Academy of Sciences, March 1999) and DeVico et al. (U.S. Pat. No. 5,843,454, see IDS).

Applicants arguments are that the De Vico reference teaches away from the instant invention "that forming a noncovalently bonded complex has several problems such as the two soluble proteins becoming uncomplexed which as the impetus of using the cross linker in the reference". Applicant's cite *In re Gurley* (CA FC) 31 USPQ2d 1130 (1994)

> ...Gurley's position appears to be that a reference that "teaches away" can not serve to create a *prima facie* case of obviousness. We agree that this is a useful general rule. However, such a rule cannot be adopted in the abstract, for it may not be applicable in all factual circumstances. Although a reference that teaches away is a significant factor to be considered in determining unobviousness, the nature of the teaching is highly relevant, and must be weighed in substance. A known or obvious composition does not become patentable simply because it has been described as somewhat inferior to some other product for the same use.

DeVico et al. indicated that the complex formation of soluble gp120 and CD4 may be dynamic in that the molecules can from a complex then dissociate and from a complex again. By bringing the two components into close proximity the complex is stabilized, in the '454 reference the DeVico et al. choose to covalently couple the complex with a chemical cross linker. In the instant invention applicants are utilizing the same complex formation that occurs

"naturally" between CD4 and gp120 (see column 2, lines 31-54 of reference '454), here applicant's have chosen to bring the two components of the complex into close proximity by tying a sting [peptide linker of sufficient length] between the molecules. The arguments of counsel cannot take the place of evidence in the record. *In re Schulze*, 145 USPQ 716, 718 (CCPA 1965). See MPEP 716.01(C). Examples of attorney statements which are not evidence and which must be supported by an appropriate affidavit or declaration include statements regarding unexpected results and inoperability of the prior art. Applicant's argue further (page 10 of paper No. 20) "applicant's suggest that if the DeVico '454 complexes were made by the methods of Chackerian et al. the Devico complexes would no longer be chemically crosslinked and thus would not function as intended." The DeVico '454 reference teaches that the interaction between the virus coat protein and the virus receptor exposes cryptic epitopes that are not present within the viral coat protein or the CD4 receptor alone (see column 2, lines 31-54). Claim 1 ('454) of the patent reads: A composition comprising: an immunogenic complex comprising gp120 covalently bonded to CD4. Webster's Dictionary (10th edition, 1998) defines a covalent bond as a chemical bond between atoms by the sharing of electrons. Neither the claims nor the specification of '454 limit the covalently bonded complex to the use of a chemical crosslinker. A peptide bond is a covalent bond because it involves the sharing of electrons. Therefore, the prior claims do not exclude the instantly claimed chimera.

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge

generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, Chackerian et al. disclose producing an auto-antibody to the "cryptic" epitope structures of CCR5 which are exposed only by the chimera. These auto-antibodies are able to prevent HIV viral entry by blocking the receptor. DeVico et al. disclose the exposure of "cryptic" epitopes which are achieved by crosslinking the complex which in essence serves to freeze the complex. The antibodies to the receptor are ale to block HIV viral entry using an alternate receptor.

In response to applicant's argument that cited art is nonanalogous art, it has been held that a prior art reference must either be in the field of applicant's endeavor or, if not, then be reasonably pertinent to the particular problem with which the applicant was concerned, in order to be relied upon as a basis for rejection of the claimed invention. See *In re Oetiker*, 977 F.2d 1443, 24 USPQ2d 1443 (Fed. Cir. 1992). In this case, both references teach the production of antibodies that are raised against epitopes, which become exposed when the receptor interacts with an antigen. The receptors of the prior art (CD4 and CCR5) are involved in the entry of HIV virus into cells. The prior art teaches two different strategies to achieve the production of antibodies that are raised against cellular receptors involved in viral entry. Applicants arguments in essence are that a single reference does not teach all the limitations, however, this not the requirement for 35 USC § 103 rejection.

To reiterate the prior rejection, the instant invention is directed to a chimeric polypeptide comprising a viral coat polypeptide from a retrovirus and a viral receptor

Chackerian et al. disclose chimeric L1-CCR5 proteins, L1 is the viral capsid protein from bovine papillomavirus type-1 and CCR5 is a cell surface receptor and a coreceptor for some HIV strains. The reference teaches that antibodies raised to L1-CCR5 were effective at blocking viral infection in M-tropic virus strain using a single cycle replication assay (p 2376, column 2, 1st paragraph). The chimera comprises viral coat sequences and viral receptor sequences, the reference makes no discussion of using spacer amino acids yet the chimera is able to form the requisite tertiary structure indicating that a spacer is not required for the structure. That conformation is an important aspect in these chimera is indicated by the fact that denatured L1-CCR5 chimeras did not induce antibody formation to CCR5, only in the context of the folded complex is there antibody production against the receptor. This is an important point because the host should ordinarily not produce auto-antibodies against a host receptor unless the receptor is conformationally changed due to the interaction with the virus. The reference does not teach a chimera of a retrovirus coat protein and a viral receptor protein linked by spacer amino acids.

DeVico et al. disclose a CD4-gp120 complex that has been covalently linked using a reactive spacer molecule. Claim 1 ('454) of the patent reads:

> A composition comprising: an immunogenic complex comprising gp120 covalently bonded to CD4; and an adjuvant composed of aluminum phosphate gel.

The patent claim indicates that the complex is covalently coupled. According to the 10th edition of Webster's Dictionary (10th edition, 1998) a covalent bond, is a chemical bond formed between atoms by the sharing of electrons. A peptide bond is a covalent bond because the amino acids are held together in a chain by the sharing of the electrons. The reference teaches using the complex as a vaccine. The reference teaches that the interaction between the virus coat protein and the virus receptor exposes cryptic epitopes that are not present within the viral coat protein

or the CD4 receptor alone (see table 1). Gp120 and CD4 have an affinity for one another and spontaneously form a complex when placed in a solution together (see column 2, lines 31-54). These complexes are dynamic and are not stable. The reference teaches that the complex between the gp120 and CD4 exposes cryptic epitopes which elicit neutralizing antibodies (see abstract). The reference does not teach using an amino acid spacer in the production of the antigenic complex.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to utilize a chimera for the production of the gp120-CD4 complex. The chimera as taught by Chackerian et al. requires the single process step utilizing affinity purification after the expression of the chimera in an insect cell. One having ordinary skill in the art would have been motivated to make a gp120-CD4 chimera to achieve the conformational complex as taught by DeVico et al. which would have the advantage of requiring less process steps in order to achieve the same function. The prior art requires purifying the CD4 and the gp120 proteins separately allowing them to interact and then chemically cross linking followed by the removal of the excess cross linker. One having ordinary skill in the art would have a high expectation of success when expressing the complex as a single polypeptide. The addition of amino acid linkers would have been obvious to the ordinary artisan in order to alleviate potential folding constraints in the chimera. Therefore, the instant invention is obvious over Chackerian et al. and DeVico et al.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ulrike Winkler, Ph.D. whose telephone number is 703-308-8294. The examiner can normally be reached M-F, 8:30 am - 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel, can be reached at 703-308-4027.

The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for informal communications use 703-308-4426.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Ulrike Winkler, Ph.D.

JAMES HOUSEL 7/14/03
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600